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# Can Mathematics and Computational Modeling Help Treat Deep Tissue Injuries?

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**Objective:** Improving the treatment of deep tissue injuries, such as burns, by the use of computational modeling, instead of by animal experiments.
**Approach:** Development of mathematical relations between various parameters and processes. Furthermore, solving the resulting problems through the use of numerical methods, such as finite-element methods.
**Results:** Using our framework, we are able to simulate wound contraction in two dimensions, in which the wound area is followed over time. Our studies indicate that the degree of contraction can be reduced if the appearance of myofibroblasts is inhibited and if their apoptosis is enhanced. Furthermore, after skin grafting, splinting procedures are to be continued as long as TG-beta like growth factor levels are significant.
**Innovation:** A morphoelasticity-based and computational–probabilistic framework for studying the evolution of burn injuries.
**Conclusion:** The current framework is able to reproduce the time evolution of the wound area as observed in clinical results for skin grafts.

**Keywords:** deep tissue injury, mathematical modeling, wound contraction, probability estimation, (myo) fibroblasts, burn injury

## INTRODUCTION

Healing of (extensive) wounds is extremely important for the survival of individuals. Wounds occur from various reasons, ranging between burn injuries, surgical wounds, pressure ulcers, diabetic wounds, and many more. Wound healing has been researched for ages and therewith many different therapies have been developed. In the ancient times, some therapies were based on procedures that are no longer applied. Examples of such treatment were based on using honey, lint, or animal grease, as one may find in the work by Murray.[1] Nowadays, surgical treatments are carried out such as skin grafting, application of dressings (based on natural products), applying bandage, sutures, and mechanical fixation. These treatments are carried out under strict hygienic conditions. For a survey of these classical treatments, the reader may consult Pereira and Bartolo.[2]

If it comes to serious (burn) injuries, then ugly red, stiff, itching, and painful scars may arise. Despite modern better treatments, still many patients are faced with long-lasting, or even life-long complications such as hypertrophic scars or contractures. Severe wounds often give rise to contraction of the tissue. This contraction is an



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evolutionary self-defense mechanism, but if the degree of contraction is too large and if it takes too long after wound closure, then contraction can lead to a loss of functioning and a loss of mobility of the joint. In this case, one speaks of a contracture. The complication of a hypertrophic scar gives aesthetic problems to the patient, which can have serious social impact and hence impair the quality of life of a patient. Hence it is important to provide appropriate care to the patient so that the degree of complications can be reduced as much as possible. Therefore, it is important to design optimal treatments for patients so that complications are avoided as much as possible. To redesign wound treatments, fundamental understanding of the underlying biological mechanisms is indispensible. This understanding can help predict possible scenarios that may arise as a consequence of a wound. The prediction of postwounding scenarios is usually done in a quantitative way and herewith the biological theory needs to be converted into quantitative relations. These quantitative relations are the backbone of a mathematical or computational (also referred to as *in silico*) model. Various mathematical studies for wound healing have arisen over the past decades, although the collaboration between (medical) biology and mathematics is not as old as the collaboration between physicists and mathematicians is. The work that we will describe in this article relies on our modeling articles.[3–8] The interested reader is referred to the aforementioned articles, where further references are given to earlier and alternative mathematical studies on several important biological subprocesses that occur in wound healing. Such subprocesses are wound closure, which is merely the closure of the epidermis at the top layer, scar formation, wound contraction, and modeling the immune reaction. The biological mechanism behind wound contraction and wound closure are completely different in the sense that wound contraction is caused by mechanical (pulling) forces that are exerted by cells like (myo)fibroblasts, whereas wound closure involves closing of a gap as a result of cell proliferation (and migration). In the case of wound contraction, it is basically the (myo)fibroblasts, which are responsible for the regeneration of collagen to uphold the integrity of the skin that pull on their surroundings and by which the skin contracts. In particular, the myofibroblasts exert the largest pulling forces.

## CLINICAL PROBLEM ASSESSED

Deep tissue injury, such as serious burn injuries, often comes with contraction of the wounded region as a result of forces that are exerted by fibroblasts and myofibroblasts, which are responsible for the production of collagen. Contractions that lead to functional disabilities are referred to as contractures. It is our aim to optimize therapies such that the likelihood of formation of a contracture is minimized. Therefore, our interest is in the formation of contractures as a result of deep tissue injury, such as serious burn injuries. Besides wound contraction, which occurs in the dermis, we are interested in the restoration of the epidermal layer postwounding.

## MATERIALS AND METHODS

We use mathematical and computational models to simulate wound closure and wound contraction. The description that we give in this article is merely qualitative than in terms of mathematical relations and equations involved. To accomplish these simulations, we use both cell-based and continuum-based models.

### Cell-Based Models

Cell-based (or agent-based) models treat cells as individual entities and hence these models are categorized as particle models. This class of models treats the migration of cells based on haptotaxis (migration in the direction of the gradient of a chemical), random walk (diffusion), mechanotaxis (migration as a result of mechanical cues) or any other migration modes. Migration is treated by the use of a set of stochastic differential equations, where the uncertainty arises from random walk. Processes like cell proliferation (division), death, differentiation, and mutation are treated as random processes based on, for instance, exponential statistical distributions. These models often involve large number of cells and thereby they become very computationally intensive. Due to the increase of the computational cost, these models are currently limited in its applicability for larger scales, but for the sake of understanding how cells react during wound contraction, and for the sake of visualization, these models are very important.

In our cell-based formalism for wound contraction, we consider the interplay of the immune system and the generation of collagen by fibroblasts. Initially the wound area is occupied by fibrin network, which is broken down by tissue plasminogen activator that is being released by the endothelial cells from the surrounding blood vessels. This is modeled by a line source around the wounded region. The ingress of macrophages into the wound area from surrounding blood vessels is modeled by considering macrophages as individual cells that appear by a Poisson random process on the rim of

the wound. The macrophages migrate toward the wound site as a result of the gradient of the platelet-derived growth factor. This is modeled by stochastic differential equations, in which the orientation of the collagen and fibrin network are incorporated. The macrophages release transforming growth factor, and this release is modeled by the use of a reaction–diffusion partial differential equation with point sources through Dirac Delta functions (distributions in the strict mathematical sense), which are solved using finite-element methods. The gradient of the transforming growth factor, as well as the orientation of the collagen and fibrin network guides the fibroblasts toward the wound site. This is modeled by the use of stochastic differential equations. Chemical sensitivity of the macrophages and fibroblast for platelet-derived growth factor and transforming growth factor, respectively, are modeled by incorporating ordinary differential equations for the fraction of receptors on the cell surface of each separate cell that are bound. The regeneration of collagen, which is oriented according to the direction of migration, is modeled by adding the right terms to the collagen orientation tensor. The forces that are exerted by the fibroblasts are modeled by adding the point forces on the boundary of the cells to the mechanical balance as Dirac Delta functions. Permanent stresses as a result of large deformations are phenomenologically modeled by adding virtual body forces over the elements in the finite-element triangularization. We refer to Vermolen and Gefen[3] and Boon *et al.*[4] for more details about our cell-based model in the framework of wound contraction.

### Continuum-Based Models

Since we are also interested in the tissue scale, we also investigate continuum-scale models that do not consider cells as individual entities, but merely consider densities of cells. These models are based on partial differential equations. Since the set of partial differential equations contains nonlinear couplings, we are not able to find exact solutions. Therefore, finite-element methods are used to approximate the solution to our partial differential equations. In the continuum-scale model, we consider the interplay between fibroblasts, myofibroblasts, collagen, and a generic signaling molecule, such as a transforming growth factor. The influence of the immune system is modeled by the presence of an initial concentration field of the generic signaling molecule with a maximum located in the wound area. The processes of migration, differentiation, death, and regeneration of (myo)fibroblasts are modeled by reaction–transport equations, in which the transport part contains diffusion (random walk) and haptotaxis (migration in the direction of the gradient of the signaling molecule). For the mechanical forces, in Koppenol and Vermolen,[8] we use a morphoelastic model for the mechanical balance. This approach permits a physics-based treatment of permanent deformations and strains, and hence this modeling framework is very suitable for the simulation of permanent contractions.

### Dealing with Uncertainty and Modeling Outcomes

As mentioned earlier, particle-based models contain stochastic (random) processes for cellular processes. Biologists often argue that it is known under what conditions and history path a cell divides, dies, differentiates, or mutates. However, when dealing with millions of cells, then it is impossible to know the time–history path over the entire lifetime of all the cells. Therefore, cellular processes are often treated as random processes. This means that each simulation represents one outcome from a random process. Random processes in daily life are throwing dices, participating in a lottery, or by considering the time period that a receptionist has to wait between two subsequent phone calls. The time period between two subsequent phone calls is a random variable, which follows a Poisson statistical distribution. Besides the randomness in the biological processes, many input values are not known either and hence parameter sensitivity analysis is crucially important here. Parameter sensitivity analysis can reveal which parameters are mostly influential to the modeling results and which parameters hardly have any impact. This can be done for both the small-scale and large-scale models. On the basis of parameter sensitivity analysis, one can determine which modeling parameters and which parts can be removed from the model so that the formalism can be simplified further without damaging the modeling results. The more influential input parameters whose values are not known well, can be varied by sampling from statistical distributions. The principle works as follows: one, for instance, takes a sample for the modulus of elasticity from a (logarithmic) normal statistical distribution. Sampling is usually done at the same time for various input parameters to obtain computed results accordingly. Here one obtains a statistical distribution of the results and therewith one can estimate the likelihood that certain scenarios develop. This approach is usually referred to as a Bayesian approach. Furthermore, this procedure can be used to estimate correlations between several parameters,

which gives insight into the dependence of parameters on each other.

Since each simulation can be interpreted as a single realization of a stochastic process, it is necessary to run multiple simulations. This running of multiple simulations based on sampling from statistical distributions is referred to as Monte Carlo Simulations. Since the number of simulation runs is always bounded because of computational cost, this implies that the estimation of the likelihood that a specific scenario occurs, suffers from statistical errors. On the other hand, a sufficient number of simulations are needed to get reliable results. The model also contains other sources of computational errors that arise by rounding (since each number is represented only by a finite number of bits), and by truncation (numerical finite-element methods contain errors as a result of finite resolution). In this sense, the modeler has to be aware of these errors when interpreting the obtained simulation results.

In the wake of simulation of wound contraction, one can typically obtain the likelihood that the wound area (or volume) has reduced to less than a predefined fraction. The severity of the contraction is quantified directly by the fraction of the area as a result of contraction relative to the initial wound area (or volume) or by the state of the tissue in the region that was injured. Hence, the modeling tools can help to estimate the likelihood that the contraction is serious. One of the future objectives of the modeling studies is to estimate the likelihood of occurrence of serious complications like contractures or hypertrophic scars under the application of wound therapies. Then, one can find the therapy with the minimal likelihood for serious complications and hence one can determine which therapy is likely to give the most successful results. Furthermore, one can also optimize the therapy with respect to minimizing the likelihood for wound complications.

## RESULTS

First we present some computational results from wound closure models. Subsequently, some results from simulation of wound contraction are presented. Finally, we summarize our findings from the computational studies that are relevant to clinical practice.

### Wound Closure

We consider both small-scale models, which, as mentioned earlier, focus on cells as individual entities and large-scale models, which are based on cell densities instead of that they track individual cells. Since cell sizes are of the order of (tens of) micrometers, this implies that one is limited to dealing with small computational domains because of computational limitations. Figure 1 shows four snapshots of a simulation of wound closure using a small-scale model. It can be seen that the gap closes, and that the increased cell proliferation makes the cell density first increase and subsequently close as a result of contact forces. Corresponding to Fig. 1, Supplementary Movie S1 illustrates the time evolution of the closing of the wound in a more dynamic way. These models are often based on measurable parameters and treat processes like cell division (cell proliferation), cell mutation, cell migration as (partly) random (stochastic) processes. More information about this model can be found in Vermolen and Gefen.[3] This model can be applied to simulate epidermal wound closure, which involves healing of the wound at the very top of the skin, that is, at the epidermis.

Larger-scale models are characterized by dealing with cell densities. Cell densities can be interpreted as a number of cells per unit area or volume (depending on a two or three dimensional treatment). As mentioned earlier, the large-scale models consist of (a set of) partial differential equations that typically can be solved using analytic or numerical techniques such as the finite-element method. A clear advantage of the large-scale models is that wounds with sizes in the order of centimeters or even larger can be simulated. These models often do not entail any stochastic processes and hence they have a deterministic nature. An example of several snapshots of such a model, for wound closure, can be seen in Fig. 2. Contour lines represent lines of equal cell density, which represents the number of cells per unit area. Values of zero and one for the cell density, respectively, represent fully wounded and fully healed (undamaged) states. A more dynamic view can be obtained from Supplementary Movie S2. At the very final stages of the simulation, the wound has closed and the legend only contains lines of cell densities that are close to one. The model used in this study is based on the Fisher–Kolmogorov equation, see for instance Adomian,[9] Adam,[10] and Sherratt and Murray.[11]

Furthermore, alternative models in the framework of cellular automata or cellular Potts models exist next to these modeling approaches. These models are lattice based, where each lattice point can represent a discrete state (such as being part of the wounded or undamaged region). These models will not be considered any further in this article.

### Wound Contraction Modeling

In one of our modeling studies, we consider a cell-based model, see Boon *et al.*[4] At the initial

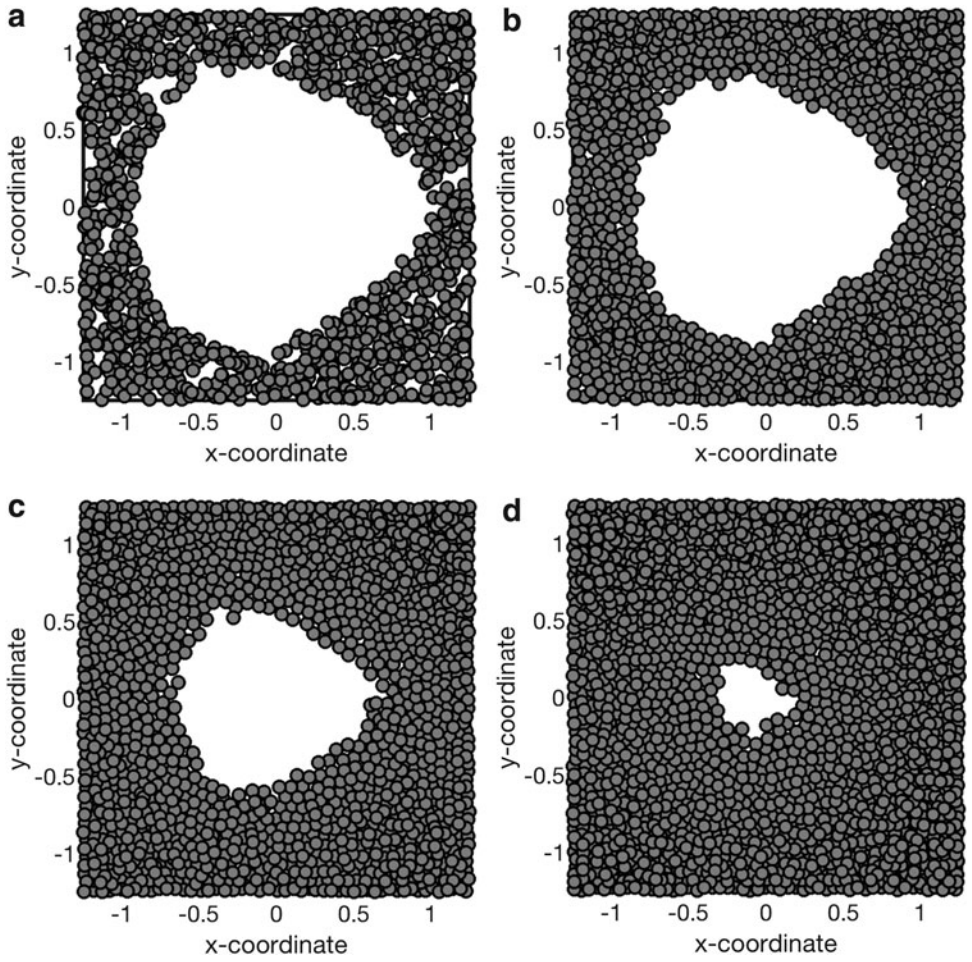


**Figure 1.** Snapshots at consecutive times from a cell-based model for simulating wound closure. The *red circles* represent the epithelial cells. Snapshots are shown at $t=0$ (initially) **(a)**, $t=10$ **(b)**, $t=50$ **(c)**, and $t=200$ **(d)** dimensionless time units.

stage of the simulation, we assume that there is a field of platelet-derived growth factor as a result of its release by the platelets that were already present in the wound region. This platelet-derived growth factor initiates the migration of macrophages toward the wound site. The macrophages migrate in the direction of the gradient of the platelet-derived growth factor. This migration in the direction of the gradient of a concentration through the extracellular matrix is referred to as haptotaxis. The function of the macrophages is to steer the immune system, which clears up the contaminants in the wound area. Next to this function, they release a chemical signal, transforming growth factor (beta), which is detected by the fibroblasts. The fibroblasts migrate in the direction of the gradient of the TG-beta toward the macrophages that are in the wounded area. The fibroblasts deposit collagen in the direction of migration so that the collagen is oriented according to the migration pathway of the fibroblasts. Next to collagen deposition, the fibroblasts pull their environment, by which the wound contracts. Plasticity has been incorporated phenomenologically so that we can model a permanent contraction. In Fig. 3, we show the positions of the fibroblasts and macrophages as well as the orientation of the collagen that is produced by the fibroblasts at consecutive times. The same dynamics is shown in Supplementary Movie S3, where one can follow the time-dependent post-trauma behavior of the skin. Of course, it should be realized that this model is only conceptual since the scale is very small despite that contractures only take place in large, deep wounds.

In our more recent studies, we consider a more realistic setting regarding burns, where we use a continuum-scale model that is suitable for larger wound regions. Here, we consider a hypothetic burn on a relatively flat body part, such as the back of a patient. Furthermore, we incorporate morphoelasticity in this simulation, which means that after a significant contraction, the skin has deformed plastically. Mathematically, this simula-

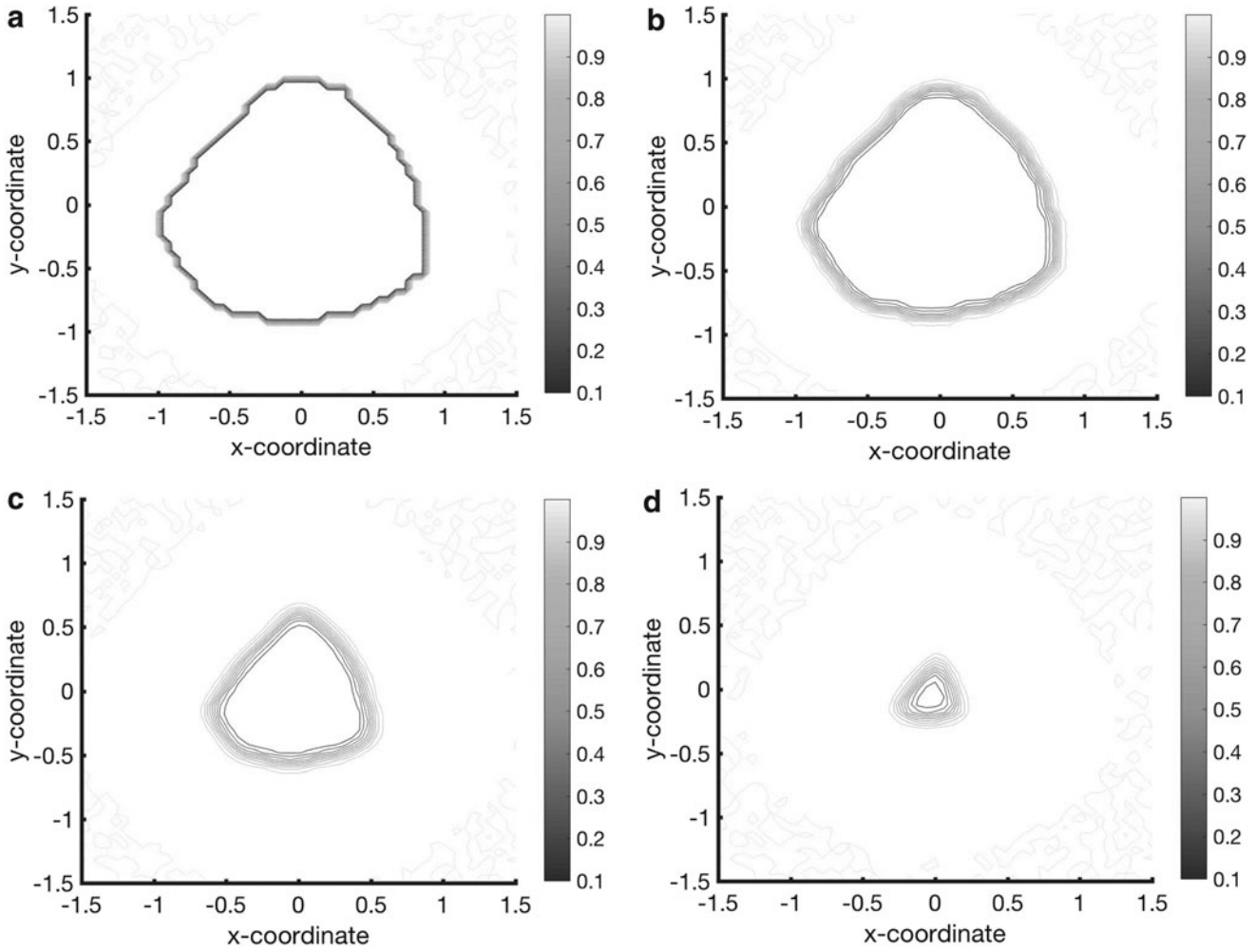


**Figure 2.** Snapshots at consecutive times from a continuum-based model for simulating wound closure. *Contour lines* represent curves at which the cell density is equal. Snapshots are shown at $t=0$ (initially) **(a)**, $t=10$ **(b)**, $t=30$ **(c)**, and $t=50$ **( d)** dimensionless time units.

tion involves three different states: the "initial" state of the tissue, "current" state as a result of fibroblasts that pull on their surroundings, and an intermediate state, which represents the "new equilibrium state" that is attained once the fibroblasts stop exerting their pulling forces. The computational setting has been sketched in Fig. 4. The difference between the "initial" state and the "new equilibrium" state characterizes the plastic deformation as a result of morphoelasticity. In Fig. 5, we show the computed normalized wound area (*i.e.*, the wound area divided by the initial wound area) of a skin graft as a function of time for several input data. Attracted by chemokines released by the immune cells, the fibroblasts migrate from the surrounding tissue into the wound region. Next to invading the wound region, they proliferate (divide), reestablish collagen, and pull on their environment. Besides these processes, the fibroblasts also differentiate into myofibroblasts, which exert larger pulling forces on their direct environment. This makes the wound area decrease. As time proceeds, controlled death of (myo)fibroblasts (apoptosis) takes place, which makes the cell forces decay down to zero. If the tissue were entirely elastic, then the wound region would transform back to its original shape. (Neo-)Hookean (traditional) mechanical models for elasticity would also predict this behavior. In our model, however, we incorporate the fact that if deformations (actually strains) are large, then the wound region no longer flows back to its original shape once cell forces cease to be active. Hence in our case, the tissue stays deformed, and hence endures plastic deformation. Traditional mechanical models in tissue engineering are based on Hooke's Law and on small strain and hence cannot be used to model plastic deformation. The horizontal axis represents time, and the vertical axis represents the normalized wound area in Fig. 5. It can be seen that as soon as

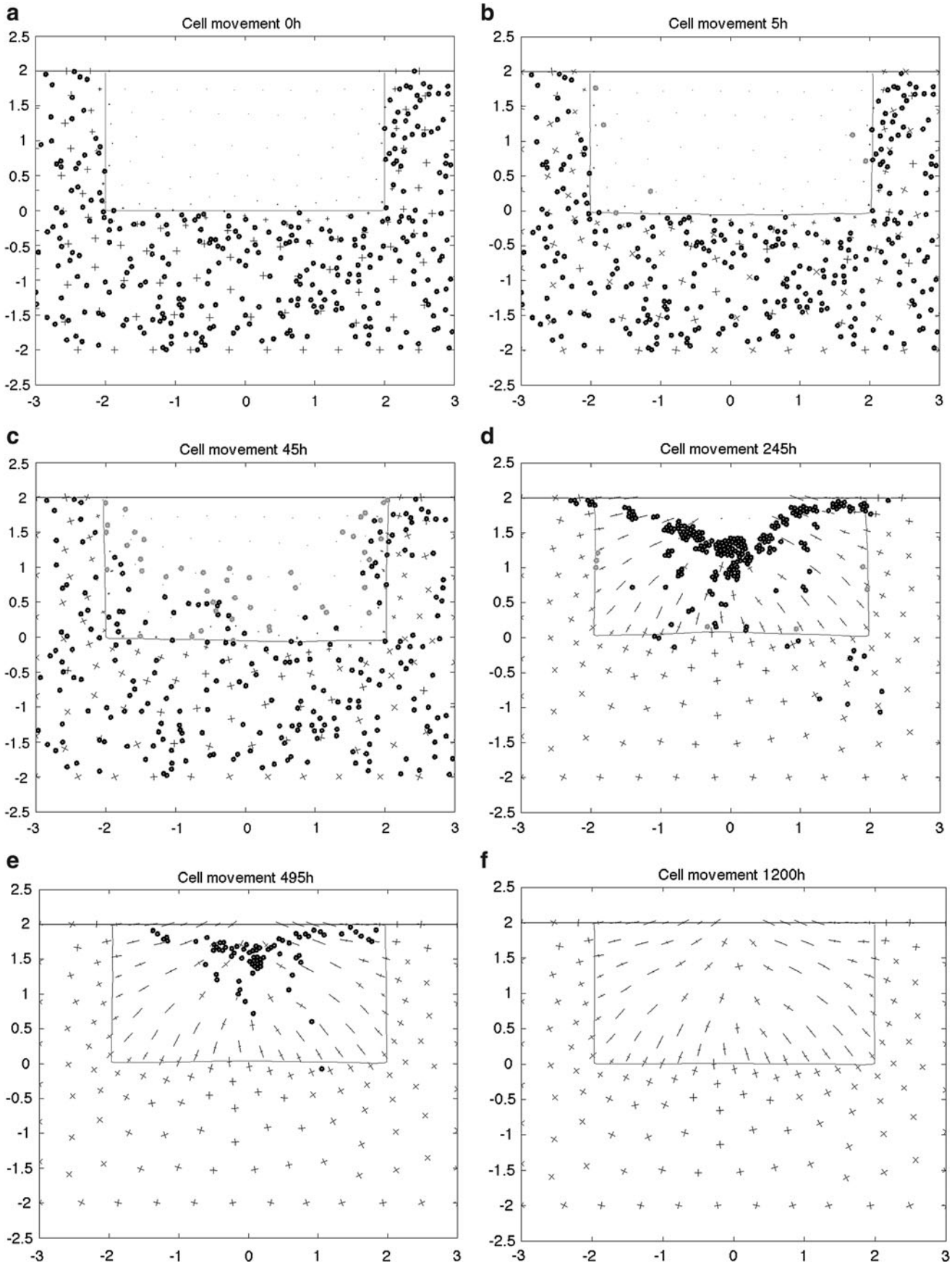


**Figure 3.** Snapshots at consecutive times from a cell-based model for wound contraction. The *blue dots* represent the fibroblasts, the *red dots* represent the macrophages. The *small blue line segments* represent the orientation of the collagen that is produced by the fibroblasts. The *contour* represents the edge of the wound. Snapshots are shown at $t=0$ **(a)**, $t=0.2$ **(b)**, $t=1$ **(c)**, $t=5$ **(d)**, $t=10$ **(e)**, and $t=24$ **(f)** dimensionless time-units. The Figure was also shown in Vermolen and Gefen.[3]

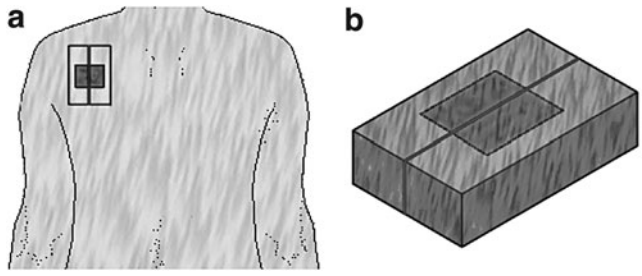


**Figure 4.** A schematic of a simulated case study of a burn injury, **(a)** represents the hypothetical location of the injury, **(b)** represents the geometrical implementation in the computational model. The figure was also shown in Koppenol and Vermolen.[8]

the fibroblasts move into the wound area, then, their contractile forces result in a contraction of the area, which can be seen by the decrease of the wound area. At later stages, the (myo)fibroblasts die as a result of apoptosis, and then the wound somewhat retracts toward its original shape, although its original shape is not fully restored. This stagnation results into a final contraction. The final contraction of the skin graft may lead to serious limitations of the patient's mobility. More information about this morphoelastic formulation can be found in Koppenol and Vermolen.[8]

Because of the uncertainty in the values of the parameters, we carried out multiple simulations to a full partial differential equation model to estimate the likelihood of having a predefined final contraction. For reasons of efficiency, these model results have been obtained on the basis of classical Hookean mechanics. The results are shown in Fig. 6. Here the vertical axis represents the likelihood that the fraction of the wound area has reached a smaller fraction than indicated on the corresponding horizontal position. This figure can be used to estimate the probability of how severe a contracture can get for a given wound. More information about the probabilistic (Bayesian) approach can be found in Koppenol *et al.*[7]

### Clinical Results

In our studies, of which the details can be found in Vermolen and Gefen,[3] Boon *et al.*,[4] Koppenol *et al.*,[5] Koppenol *et al.*,[6] Koppenol *et al.*,[7] Koppenol and Vermolen,[8] we have observed that it is advantageous to keep counts of myofibroblasts as low as possible by either inhibition of formation of myofibroblasts or by stimulating myofibroblast apoptosis (programmed cell death) to prevent large

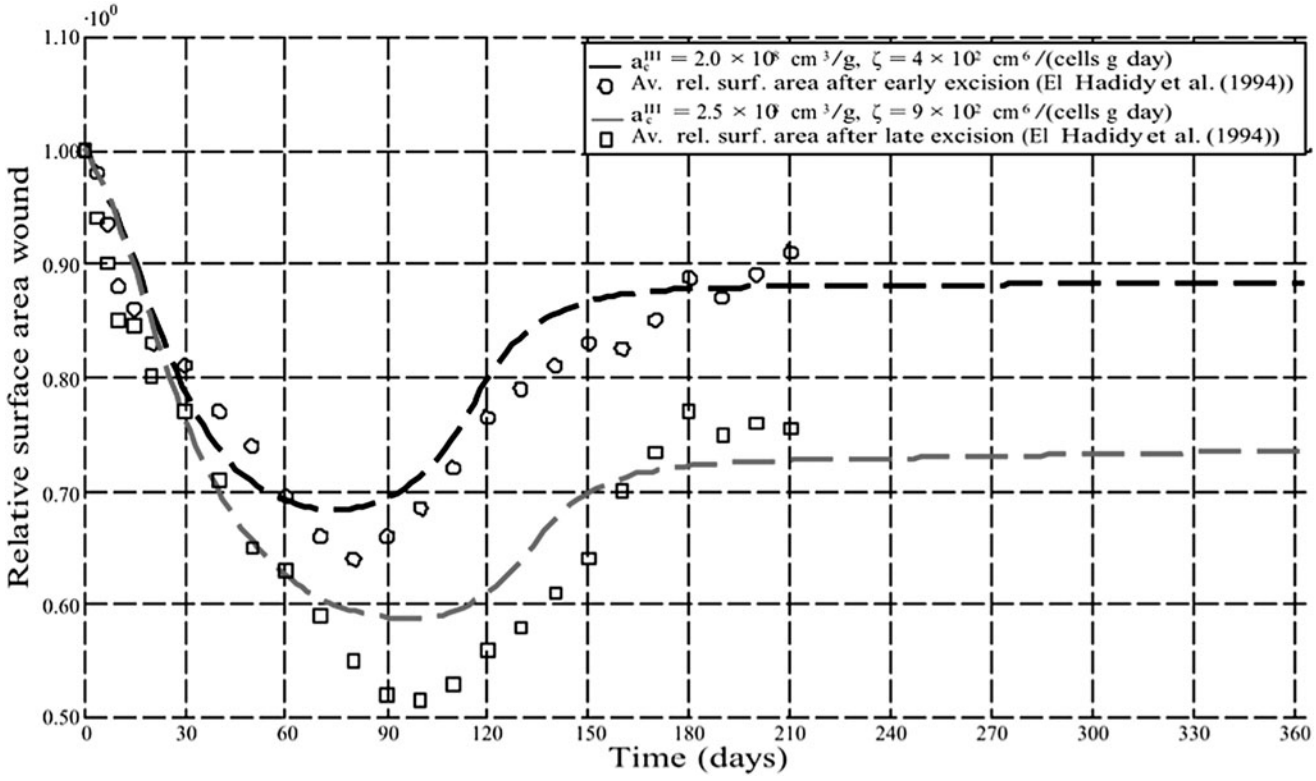


**Figure 5.** The wound area versus time for the morphoelastic model for several input parameters in comparison with experimental outcomes on skin grafts (by Hadidy *et al.*[12]). This figure was also shown in Koppenol and Vermolen.[8]

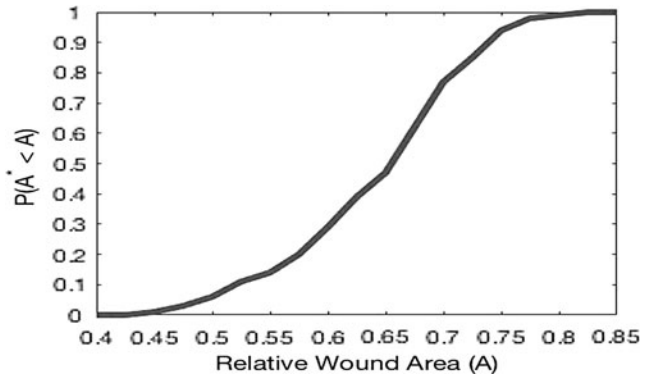


**Figure 6.** The cumulative probability of having a wound contraction with area reduction, A*, of more than a certain fraction A. The *horizontal axis* represents the fraction of area, the *vertical axis* represents the cumulative probability, which is the probability that the wound contracts to a fraction of area, A*, that is smaller than the fraction, A, on the *horizontal axis*.

contractions. Furthermore, since permanent contraction is formed by a combination of pulling forces and growth factors, splinting should be applied immediately after skin grafting, and to be continued as long as the levels of signaling molecules (such as transforming growth factor beta) are significant.

A shortage of macrophages (*i.e.*, the immune system is inhibited) gives a delayed wound healing, which is a bad thing, but it also inhibits wound contraction, which can be beneficial to the patient. Furthermore, in our models,[3] we observed that blocking of receptors on (myo)fibroblasts (which stimulate regeneration of collagen and migration) can reduce contraction. This reduction can possibly be realized by treatment with TG-beta antagonist.

## DISCUSSION

Our modeling frameworks can be used successfully to quantitatively reproduce important trends from clinical settings as has been confirmed by a good fit between our computational framework and the measurements by El Hadidy *et al.*[12]

Despite this successful use of the models, one should bear in mind that (mathematical) models are constructed on the basis of assumptions of how the process impacts its environment and how it behaves and evolves. This immediately reveals a limitation of each model since a model is the modeler's representation of reality. Processes, like wound contraction or wound healing, are extremely complicated, and hence it is impossible to incorporate all the aspects of these processes into a mathematical model. Therefore, one has to distinguish between important matters with a high impact on the process and matters with a lower impact. Herewith a model is a simplified representation of reality. The most challenging task is to simplify reality as much as possible, but such that the most important features are still taken into account.

Simplification is necessary because of the following rationale: Suppose that we have a perfect mathematical model, which takes into account all the processes in wound healing. Then we would have to understand all facets of wound healing. Currently, the biology behind wound healing is understood to a large extent, nevertheless still many open questions remain. However, we imagine that we know everything and that we have a complete model. (Dermal) Wound healing is a complicated process in which mechanics, chemistry (think of the interplay between cells and chemical elements [chemokines, growth factors, oxygen, nutrients]), and collagen development (produced by fibroblasts ["skin cells"]) play an important role. Incorporating all these issues results into a complicated model. Such a complicated model requires the use of a large number of input variables. This large number of input variables is a big issue, since the values of these numbers are not known exactly. In fortunate cases, one can find some values in the literature, where they have been measured. However, it is not likely to find measured data for all the input values to the model that has been constructed. The reason is that these parameters were never measured because until now it made no sense to investigate them.

Measurements always contain uncertainties, and after reproducing the experiments, one obtains confidence (mostly 95%) intervals for the measured data. Using these data in a mathematical model makes that a source of uncertainty is introduced into the modeling. Furthermore, many parameters that are relevant in wound healing models, one may think of a Young's modulus, cell division rates etc., vary from patient to patient, depending on sex, age, race, lifestyle, and genetic heritage. This immediately introduces another source of uncertainty. Parameters that are new to the model and that have never been measured introduce an additional uncertainty and hence the model needs to be calibrated with clinical data. This technique is commonly referred to as inverse modeling, where a set of parameters is adjusted such that a mathematical model gives an optimal fit to measured data. In all these cases, the models go with uncertainty, which should be dealt with by the modeler.

Since clinical data are not always available, animal studies and *in vitro* models are often used for calibration of the models. The use of animal experiments can be considered as questionable since it is not always clear to what extent experiments on, for instance, mice reflect wound healing in the skin of humans. It should be noted that animal experiments are, like mathematical models, also just representation, or models, of wound healing of human skin. Hence, it is not immediately obvious whether these experiments can be used to calibrate the mathematical model. Clinical measurements on patients are a much better source for use of calibration than animal experiments, and therefore, it would be very advantageous if practitioners encourage patients to give consent for scientific use of data derived from them.

As noted earlier, models are a representation of reality, and the model is designed to fit the needs of the community that uses the model. The objective of a model can be the following:

- To understand as much as possible the biological mechanism behind wound healing;
- To predict how different scenarios develop postwounding;
- To visualize and illustrate a (biological) process;
- Any combination of the earlier-mentioned points.

If the objective is to understand the biological mechanisms as much as possible, then the model should incorporate a high level of detail and hence the model becomes complicated. This class of models, despite their high level of physics involved, is known to be complex and to include very many (uncertain) input parameters. The other class of models, which merely aim at being predictive, may be better off being less physically sophisticated and hence by taking a lower degree of detail into account. This model is then able to interpolate between different clinical scenarios so that the available dataset is used in an optimal way. Here, calibration of the model remains crucially important. The models that incorporate fewer physical assumptions are often referred to as phenomenological models. These models often contain only few input parameters and a relatively simple mathematical problem to solve. Hence simulations can be done within a short computation time, and this makes the model very suitable for a swift prediction of postwounding scenarios and calibration is usually done in an easy way.

An important take-home message is that a more complicated, sophisticated model is not necessarily a better model.

All these things were simulated in a quantitative way, by which the potential of computer simulations to describe the time evolution of a burn injury has been illustrated. We realize that the current results are still in the preliminary phase, but we expect that in the future, doctors can scan a wound and then run the simulation tool to estimate the likelihood for complications that the patient will face if treated or untreated. Many of the results have been computed in a two-dimensional setting, which means that many of the geometrical issues have not been dealt with properly. Furthermore, the simulations still require a large computational time, which makes the simulations unsuitable for Monte Carlo methods, in which many computations need to be done. Monte Carlo methods also need to be implemented in a clever way such that fewer simulations are necessary if the resolution of the finite-element method is higher. All these things are for future research as well as the incorporation of therapies in the simulations. One of our models has been validated against experiments on humans, see the work by El Hadidy *et al.*[12] There is development in the legislation that practitioners are supposed to document wound characteristics at different times. This development will generate more clinical data and herewith more accurate predictions for wound evolution can be realized in the future.

Different patients invoke different parameter values and this uncertainty needs a probabilistic treatment of the simulation model. In case of simulating the behavior and time evolution of burn injuries in relation to the development of complications like hypertrophic scars or contractures, we do not believe in the power of a single simulation outcome. This disbelief is caused by considering a simulation as just one single probabilistic experiment, which is commonly rejected by experimental physicists, who also carry out multiple experiments to sustain their hypotheses. From a clinical perspective, it becomes more and more interesting to estimate the likelihood that certain phenomena take place rather than just simulating the phenomenon as such. The role of modeling in determining the likelihood of phenomena to occur can be important. Inserting therapies will be a matter of changing the input parameters and boundary conditions in the models, and therewith the impact of virtual treatments can be evaluated in a quantitative way on these phenomena, and hence mathematical modeling can help improve therapies for treatment of deep tissue injuries.

## INNOVATION

The current study reports successful use of computational models for the prediction of skin evolution after deep tissue injury. A morphoelastic computational modeling framework has been established to describe the result of a permanent contracture as a result of a burn injury. The assessment of the quantification of uncertainty and the subsequent estimation of likelihood to predict a contracture with predefined characteristics has been realized. Some therapy settings were implemented into the computational models through the adjustment of boundary conditions for the partial differential equations.

## KEY FINDINGS

- A computational framework has been developed based on cell-based and continuum-based principles for modeling wound closure and contraction on a small and large scale, respectively;
- A Bayesian framework has been established to assess the likelihood that contractures develop postwounding to a predefined extent;
- Computational studies reveal that splinting should be done immediately after grafting and that splinting should be prolonged as long as levels of signaling molecules (for instance transforming growth factor beta) are significant.

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## AUTHOR DISCLOSURE AND GHOSTWRITING

F.V. did most of the typesetting. P.Z. read the article carefully and gave some feedback for improvement. The computational models (including the computer codes) to simulate wound closure were developed by F.V. Part of this article entails a compilation of articles about wound contraction that were earlier written by Daniel Koppenol and Wietse Boon and coauthored by P.Z. and F.V. These two aforementioned projects were done under the supervision of Frank Niessen, P.Z., and F.V. No competing financial interests exist. The content of this material was expressly written by the authors listed. No ghost writers were used to write this article.

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## SUPPLEMENTARY MATERIAL

Supplementary Movie S1
Supplementary Movie S2
Supplementary Movie S3

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